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Evolution and the Ethics of Animal Research

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Evolution and the Ethics of Animal Research

Introduction

Questions about the ethical human treatment of animals ultimately focuses on two issues: animals as food, and the use of animals as subjects in scientific experiments. In both cases, arguments have centered on questions about the moral status of animals, and the benefit to humans of such uses. In the second of these two classes of cases, discussion has increasingly focused on different areas of research where animal subjects are used: toxicology, pharmacology, and investigation into specific diseases (among others). In each area, benefits to humans in using animals as experimental subjects differ both in their degree of certainty and of their extent. Both factors are relevant to moral deliberation if it is admitted that calculations of benefit to humans (and animals) are morally relevant at all. The use of animals as experimental subjects in all these areas assumes, however, that animals are reliable analogs of humans in causally relevant ways. We will argue that a fuller appreciation of the implications of evolutionary theory for moral reflection about the use of animals as scientific experimental subjects actually significantly narrows the range of cases where moral considerations are paramount—that is, cases where some real benefit to humans or other animals might be thought to morally justify discounting animal pain (pain and suffering endured by animals as experimental subjects). Our contention is first that in areas such as toxicology, pharmacology, and the investigation of specific diseases, appreciating the fuller implications of evolutionary biology leads us to question the reliability of animals as causal analogs to humans. If it cannot be established that the specific animals that researchers propose using as experimental subjects are, in fact, reliable causal analogs, it is impossible to reliably calculate any purported benefit to humans. Moral arguments that "weigh up" benefits that are uncertain at best against certain animal pain and fatality are, by any measure, exceedingly weak as a foundation for a moral justification for using the animals in question as experimental subjects.[1] It is clear to us that in all such cases, the uncertainty of benefits to humans, should, (however one feels about the morality of using animals as experimental subjects) constitute overriding reason to prefer alternative experimental protocols. The only ethical justification in such cases would have to consist in an appeal to arguments that animals lack 'moral standing' altogether. On such a view, even if no certain or likely benefits to humans can be identified, it is simply not wrong to "sacrifice" them or cause them pain. But even defenders of using animals as experimental subjects in ways that are unavoidably painful or fatal to them typically balk at such arguments. And since experiments with only an off-chance of benefit to humans in the gain of knowledge are fundamentally bad science, we do not propose to discuss such cases. Moral considerations come into play when there is every good reason to believe that the animals which researchers propose to use *are* reliable causal analogs of humans—and, thus, that there is an identifiable and more or less certain benefit to humans.

The first part of this paper will review some implications of recent scientific research with a view to clarifying its implications for purported calculations of benefit to humans of several uses of animals

as experimental subjects. The second part of this essay seeks to clarify the moral implications of questions raised by evolutionary biology about the reliability of animals as causal analogs to humans. We think that experimentation on animals of any kind (certainly the usual mammalian suspects) carries with it a heavy moral burden of proof for those who propose to use animals as experimental subjects in ways that are painful and/or fatal. Agreeing with Baruch Brody (2001) that any plausible moral argument for the permissibility of using animals as experimental subjects must defend "discounting" animal pain, we will argue that uncertainty about the reliability of animals as analogs of humans makes a clear argument for discounting impossible. (Note that Brody (2001) defines "discounting" as the notion that "the same unit of pain counts less, morally, if it experienced by an animal than it would if it is experienced by a human being". Without being able to identify a clear benefit to humans, typically a benefit that remediates human suffering that can presumably be expressed as a quantified "cost", it is impossible to identify any "quantity" or "unit" of animal pain with which to compare or "weigh" it in an analysis of cost and benefit. So experimental protocols that involve using animals as experimental subjects in way that will be painful to them, but that cannot point to a clear remedial benefit to humans, really only "weighs" (and only appears to "weigh") a very calculable cost to animals against a *chance* that humans *might* benefit. This, however, if it were genuinely a "calculation" (a "weighing" of cost vs. benefit) would be a calculation of probability—a calculation that the implications of evolutionary biology that we call to attention make unpromising scientifically and morally fraught. In other words, what can, at best, be a projection of possible utility is far from the sort of calculation of utility that would be required as a moral justification for discounting animal pain where animals are to be used as experimental subjects. In our conclusion, we point to the serious moral risk (and a contradiction inherent) in posing (in the most literal sense) utility as a moral justification for what is ultimately only a disregard of animal pain.

Are Mice "Men Writ Small"?

In the US somewhere between 14 and 16 million animals are used in biomedical research each year. The vast majority of mammals (85 to 90 %) employed in biomedical research aimed at benefiting humans are rodents (Shanks 2002, p. 172). Primate species do not make up a significant part of the total partly because they are difficult and expensive to house, and partly because, in the case of such species as gorillas, chimpanzees, and orangutangs, they are close to extinction.

Nonhuman mammals are employed in biomedical research because there is a strong conviction by biomedical researchers that notwithstanding obvious morphological differences between humans and (say) rats and mice, rodents are sufficiently similar to humans in biologically relevant respects to support the extrapolation to humans of results found in rodents. It is on the basis of claims about the reliability of such extrapolations that great human benefits are said to flow from research on mammals. Nonhuman mammals are thus acknowledged to be different in some respects from humans, but similar enough in other respects to be valuable research subjects. The problem here is that claims about the significance of similarities and differences between humans and the animals used to model their biology are not settled matters concerning which there is a general scientific consensus.

In the last twenty years, prompted at least in part by observations of the enormous medical consequences of rapid bacterial evolution in response to widespread and irresponsible use of

antibiotics, there has been a growing interest in the implications of evolutionary biology for human medicine (see Ewald 1994, Nesse and Williams 1995, Lafollette and Shanks 1996, Trevathan et al., 1999, Greaves 2000, Frank 2002). The theory of evolution is our current best theory concerning similarities and differences between members of a given species (the issue of intraspecific variation) as well as similarities and differences between members of distinct species (the issue of interspecific variation).

How, then, is evolutionary biology relevant to a discussion of the use of animals in biomedical research aimed at benefiting humans? As we will see below, scientific investigations into the significance of both intraspecific variation and interspecific variation call into question the reliability of extrapolations from rodents to humans in ways that are relevant to a cost-benefit analyse that may be thought to justify discounting animal pain.

In terms of the pattern of evolutionary relationships, the line leading to modern humans seems to have diverged from the line leading to modern rodents about 70 million years ago (for some140 million years of independent evolution), whereas the line leading to modern mice seems to have diverged from that leading to modern rats some 17 million years ago. Rats and mice are more closely related to each other than either is to humans.

From a genetic point of view the human genome project has revealed that the human genome consists of some 30,000 genes. The mouse genome is about the same size as the human genome (Boguski 2002). Moreover, reflecting common ancestry, counterparts (orthologs) of many human genes have been identified in both mice and rats (notwithstanding differences in chromosomal arrangement). From the standpoint of genetic “base-pair similarity,” humans, rats, and mice are remarkably similar. But the devil of genetic differences between individuals of a given species, as well as genetic differences between members of different species, lies in the details.

Mammals are diploid organisms and this means they have two sets of chromosomes, one from each parent. Such chromosomes in a diploid individual are said to be homologous in that they have the same pattern of genes along the chromosome. The location of a given gene on a chromosome is known as its *locus*. For a given locus, different versions of a gene – known as alleles – may exist in a population. Such allelic variation generates variation with respect to the genotypes found in a population, and is thus a source of genetic polymorphisms.

Though each individual has two alleles at a given locus, one from each parent, a large population of such individuals may exhibit several alleles for a given gene, and these will be found with various relative frequencies in the population. Different alleles typically have different biological properties. When these properties influence the reproductive success of the organisms bearing them with the effect that different organisms in the population leave behind different numbers of offspring, then evolution by natural selection occurs, and this has the effect, over successive generations, that the frequencies with which given alleles are found in populations changes (allele frequencies can change for other reasons too, but this need not concern us here).

The main implication of evolutionary biology for our inquiries is the uncontroversial observation that in natural populations (e.g., of mice or humans), there is typically variation with respect to the alleles that are present. Typical laboratory populations of (say) mice are represented by highly inbred strains or varieties. The value of an inbred strain is supposed to lie in its relative genetic

homogeneity. The hope is that individuals belonging to such strains should respond similarly when similarly stimulated (perhaps with drugs or toxins). The use of highly inbred individuals is thus a way to control for the real genetic variation in natural populations which can confound the results of laboratory experiments. The problem of interspecies extrapolation from rodents to humans (where there are genetic similarities, but not genetic identities) is thus exacerbated by the fact that human populations will often not only contain alleles very different from those in rodent populations (where similar genes can be identified), but will also typically exhibit allelic variation that is absent in the (homogeneous) laboratory rodent populations used to model them.

We propose to illustrate the importance of these observations by considering first the known effects of allelic variation in humans with respect to drug metabolism; second the problem of extrapolating from rats to mice (and vice-versa); and third the problems of extrapolation from rodents to humans (with respect to drugs, toxins and diseases such as cancer). This illustration forces us to acknowledge the very real difficulty in establishing a certain benefit for humans to be gained by using rats and mice as test-subjects with respect to a wide range of drugs, and as tests for toxicity and carcinogenicity.

The enzyme system playing an important role in xenobiotic (drug and toxin) metabolism is the cytochrome *P450* system. Some 500 *P450* enzymes have been characterized in terms of DNA sequences, members of a given species may carry 40 -50 (Guengerich 1997, p. 162). Cytochromes P450 will be abbreviated to CYPs for ease of reference.

First some terminology. The CYPs form a superfamily of genes. The following example will help with the nature of CYP nomenclature. Consider CYP 1A2. The first number designates the family the gene belongs to, and this is determined on the basis of at least 40% sequence similarity. The letter designates subfamily, determined on the basis of at least 59% sequence similarity. The last number identifies the gene (or protein). CYP 1A2 and CYP 3A4, for example belong to different families constitutive of the CYP superfamily. By contrast, CYP 2C9 and CYP 2D6 belong to different subfamilies of the same family. Specific alleles may be denoted by an additional number and an asterisk. CYP2D6*10 refers to a specific allelic variant of CYP2D6, and so on.

(i) Human intraspecific variation.

We all too readily speak of mice and humans as if all mice and all humans were the same. This is an error from an evolutionary perspective, for there are differences in the form of heritable variation within identifiably different populations. In humans CYP polymorphisms can manifest themselves in the form of intraspecific differences in drug metabolism. Two genes, CYP2D6 and CYP2C19 are particularly important since they affect how people metabolize approximately 25% of the drugs on the market (Eliot Marshall 2003, p. 589).

Sipes and Gandolfi (1993) observe that with respect to the antihypertensive agent debrisoquine, some 3 to 10 percent of Caucasians are poor metabolizers because they are homozygous for 2 nonfunctional alleles for CYP2D6 (the source of debrisoquine 4-hydroxylase). There appear to be more than 75 allelic variants of CYP2D6 circulating in human populations (Weinshilboum 2003, p. 532).

There are ethnic differences in the distributions of these alleles: individuals homozygous for the *10

allele, for example, have low CYP2D6 activity and make up nearly 20% of the Japanese population – a figure that differs from both Caucasian and Chinese populations (Tateishi et al., 1999, p. 581). Studies in molecular genetics indicate that causality is complex among those exhibiting little or no CYP2D6 activity. Causal factors range from single nucleotide polymorphisms in the protein coding sequences, to deletions of the gene itself, to polymorphisms affecting the splicing of CYP2D6 (Weinshilboum 2003, p. 232). On the other side of the coin, there are rapid metabolizers who possess duplicates of the CYP2D6 gene (some with as many as thirteen copies), and who thus require more than the standard doses of drugs to achieve therapeutic responses. It hardly needs to be pointed out that these important differences could never have been revealed by nonhuman animal studies.

In the case of the antiepileptic drug mephenytoin, more than 20% of the Japanese population are poor metabolizers (compared to about 3% of the Caucasian population) (Sipes and Gandolfi 1993, pp. 95-96). Enzymes in the CYP2C subfamily have been shown to be responsible for mephenytoin metabolism, with CYP2C19 being the main (S)-mephenytoin 4'-hydroxlase (Guengerich 1997, p. 167). The poor metabolizers appear to make a stable, but defective protein (Sipes and Gandolfi 1993, p. 96). The presence of CYPC19*2 and *3 alleles account for 99% of oriental poor metabolizers and 87% of Caucasian poor metabolizers.

These examples represent only a small sample of what is known about polymorphisms with respect to the specific enzymes and substrates mentioned. But they highlight the importance of paying attention to intraspecific variation when considering metabolic activity. Partly for these reasons Collins has recently pointed out:

> In the field of metabolism, as well as some segments of toxicity and efficacy, there has been a major shift from animal-derived data to human-based data. Except for comparative studies to assess interspecies differences, animal studies have declined in importance. Part of this shift is driven be an appreciation for the uncertainty in cross-species metabolic pathways. From the practical side, the well-organized, readily available supply of human tissue has fueled this shift (2001, p. 238).

The existence of intraspecific variation is but a foretaste of the biological problems confronting those who seek to use animals to model human biomedical phenomena. As Darwin observed in the *Origin of Species*:

> As each species tends by its geometrical rate of reproduction to increase inordinately in number; and as the modified descendants of each species will be enabled to increase by as much as they become more diversified in habits and structure, so as to be able to seize on many and widely different places in the economy of nature, there will be a constant tendency of natural selection to preserve the most divergent offspring of any one species. Hence, during a long continued course of modification, the slight differences characteristic of varieties of the same species, tend to be augmented into the greater differences characteristic of species of the same genus (1972, p. 108).

In other words the effect of evolutionary processes, in the formation of new species, is essentially to amplify the differences that existed in the varieties constitutive of the common ancestor from which the new species descend in the course of evolutionary time. Interspecific variation is thus likely to

be more of a problem for the animal modeler than the already confounding intraspecific variation we have just discussed.

(ii) Extrapolation between rodent species.

As noted above, rats and mice are more closely related to each other than either is to humans. While intraspecific variation is important within rat and mouse populations – marked differences exist with respect to drug metabolism and susceptibility to diseases such as cancer between different strains of mice and different strains of rats – interspecific extrapolation between rats and mice has proved to be no simple matter. Rats are not particularly good models for mice! Thus as Hoffman has observed:

> Correspondence between mouse and rat, the two most commonly used species in carcinogenicity tests, is not especially high. For 73 compounds evaluated by Tennant *et al.*, the concordance between mouse and rat was 67%. Moreover, in an evaluative study by Griesemer and Cueto, only 44 of 98 agents that were carcinogenic in either rats or mice were carcinogenic in both species (1993, pp. 216-217).

(iii) Extrapolation from rodents to humans.

There is an enormous literature on the problems associated with extrapolation from rodents to humans. We will briefly examine two examples to highlight the difficulties encountered in this enterprise.

(a) Cancer.

Alberts *et al.* , point out in *The Molecular Biology of the Cell* (one of the leading textbooks in molecular biology):

> The mouse is the most widely used model organism for the study of cancer, yet the spectrum of cancers seen in mice differs dramatically from that seen in humans. The great majority of mouse cancers are sarcomas and leukemias, whereas more than 80% of human cancers are carcinomas – cancers of epithelia where rapid cell turnover occurs. Many therapies have been found to cure cancers in mice; but when the same treatments are tried in humans they usually fail (2002, p. 1347).

There are 26 known human carcinogens (the list of probable carcinogens is somewhat longer.) Of these 26 carcinogens, humans are exposed to 7 by inhalation. Do carcinogenicity assays involving rodents convey information about human risk? Two decades ago, Salsburg observed of the 26 known human carcinogens:

> Most of these compounds have been shown to cause cancer in some animal model. However, many of the successful animal models involve the production of injection site sarcomas or the use of species other than mice or rats. If we restrict attention to long-term feeding studies with mice or rats, only 7 of the 19 human non-inhalation carcinogens (36.8%) have been shown to cause cancer. If we consider long-term feeding or inhalation studies and examine all 26, only 12 (46.2%) have been shown to cause cancer in rats or mice after chronic exposure by feeding

> or inhalation. . . On the basis of probability theory we would have been better off to toss a coin (1983, p. 64).

The study of the risks posed by caffeic acid (3, 4-dihydroxycinnamic acid) contains many lessons relevant to the present discussion. In rats, 50% develop cancer when exposed to 300 mg/kg of body weight. This is known as the TD_{50}. (For mice the TD_{50} value is 4900 mg/kg of body weight (Gold *et al.*, 1992)). Because both rats and mice develop carcinomas of the forestomach, the IARC considers caffeic acid to be a possible human carcinogen. In terms of the Human Exposure Rodent Potency (HERP) index, the rat, being the more sensitive species, is used in the calculation of possible cancer hazard. The method is as follows:

> HERP (%) = 100(human dose in mg/kg) / (rodent TD_{50} in mg/kg).

A HERP value of 1% is a dose where humans are exposed to 1% of the TD_{50} for the sensitive rodent. Typical human exposure to caffeic acid in coffee alone has a HERP value of 0.1% (Gold et al. (1992)).

A typical human dose of caffeic acid from all sources is about 70 mg per day (it is in the coffee, fruits and vegetables we enjoy). This is approximately 1 mg/kg of body weight. Using rat data employed in the HERP calculation, the risk of cancer at 300 mg/kg is 1 in 2. Making the assumption of linearity (direct proportionality of dose to response), we get an extrapolation of human cancer risk as (0.5 x 1/300), i.e. 1 in 600. Harris has wryly observed:

> If caffeic acid were to come under regulatory scrutiny what probable regulatory limit would be recommended? According to the linear model it was calculated that for our average daily dose of about 1mg/kg, the estimate of cancer risk would be 1 in 600. For a regulatory one-in-a-million risk target the safe level for humans would be a dose at least 1,000 to 10,000 times lower than the actual doses we receive. . . Regulators are not mandating dose limits. The lack of attention is appropriate but for reasons that are not consistent with widely used but unrealistic linear dose to risk conversions (1997, p. 90)

In the IARC evaluation of caffeic acid (*Summaries and Evaluations*, vol. 56, 1993, p. 115), it is noted that there is no relevant human data, the threat of carcinogenicity is derived from rodent studies and the additional claim that humans and rodents metabolize caffeic acid to the same metabolite. The IARC's line of reasoning is precisely what one would expect if rodents were being used as causal models for the human condition. (Web searches actually reveal numerous sources, including the USDA, that list many healthful benefits forthcoming from caffeic acid in the diet. The USDA's agricultural research service actually points out that caffeic acid has useful antioxidant and antiviral properties). Should we be worried about caffeic acid? Probably not, especially in view of the fact that rodents have exhibited carcinogenic responses to 19 out of 20 human probable non-carcinogens (Lave et al, 1988, p. 631).

(b) Diabetes.

It has been shown that xenobiotics induce transcription of certain families of CYPs by activating nuclear receptors. CYP 3As, for example, are regulated by the pregnane X receptor (PXR). Studies have been performed on human (h) and mouse (m) orthologs of PXR. Moore *et al.* commented

upon the results of these studies as follows:

> However, comparison of PXR from four different species shows that this receptor has diverged considerably in the course of evolution. The human, rabbit and rodent PXR are all roughly equally divergent and share only ~70% amino acid identity. This divergence in PXR is an important component of cross-species differences in the regulation of CYP3A expression by xenobiotics (2000, p. 15126).

Species difference are thus not just associated with protein evolution of the structures of CYP enzymes, they are associated with evolution in the molecules that regulate the expressions of the genes coding for those enzymes as well. The regulatory role of PXR is indeed medically significant.

The CYP 3A family is particularly important in the context of xenobiotic metabolism because, as Jones et al., have noted:

> The CYP 3A gene products are among the most abundant of the monooxygenases in mammalian liver and intestine. In humans, CYP 3A4 is involved in the metabolism of more than 50% of all drugs as well as a variety of other xenobiotics and endogenous substances, including steroids (2000, p. 27).

One drug that is of interest in this regard is troglitazone, marketed as Rezulin, and used in the treatment of type-II diabetes.

Troglitazone was removed from the market in the US in March 2000. Despite the fact that it had been shown to be safe and effective in rodent studies (Jones et al., 2000, p. 36), more than 65 people died (two thirds were women), and many other required liver transplants as a result of Rezulin toxicity. In clinical trials involving a total of 2500 human subjects, about 2% showed alanine aminotransferase (ALT) levels more than 3 times the upper limit of normal. ALT levels this high are an indicator of active liver disease (see Greek and Greek 2002, pp. 114-119 for more details of how Rezulin came to market on the FDA “fast track”).

The class of drugs to which troglitazone belongs was developed using rodent models of insulin resistance, but without prior knowledge of the cellular target (Jones *et al.*, 2000, p. 36). It is now known that troglitazone achieves its therapeutic effects by binding to the PPARg nuclear receptor. But at the concentrations required to activate PPARg, it also activates PXR in humans – something it did not do in rats and mice (Jones et al., 2000, p. 30). One immediate consequence of this species difference is that in humans, patients taking troglitazone experience increased CYP3A4 activity. Jones *et al.*, comment:

Our data showing that troglitazone activates human PXR at concentrations similar to those required to activate PPARg provide an explanation for its interactions with other drugs, including oral contraceptives. Interestingly, the relative lack of activity of troglitazone on the mouse or rat PXR may explain why these effects were not reported in animal toxicology studies. Additional studies will be required to determine whether PXR also plays a role in the hepatotoxicity observed with troglitazone. In this regard it is interesting that that the PXR ligand rifampicin has also been associated with hepatotoxicity in humans (2000, p. 36).

(Recently, it has been argued that the increased CYP3A4 activity associated with troglitazone activation of human PXR results in the metabolism of troglitazone to a reactive quinone which has been hypothesized as the cause of hepatotoxicity (Willson and Kliewer, 2002, p. 262)). While examples like this could be multiplied, the point is made if it is understood that at the molecular level of life there are medically significant differences between species. These differences arise from evolved differences in catalytic activity of enzymes, or from evolved differences in the regulation of gene expression. The consequences of the belief that humans and rodents are the same molecular animal dressed up differently can be (and have been) catastrophic. As Goldstein recently put it in an editorial in the *New England Journal of Medicine*:

> One of the most striking features of modern medicines is how often they fail to work. Even when they do work, they are often associated with serious adverse reactions. Indeed adverse reactions to drugs rank as one of the leading causes of death and illness in the developed world (2003, p. 553).

While it would be wrong to say we have learned nothing about humans from animal experiments (except, perhaps, how different we are from our common animal models), it is a consequence of the foregoing discussion of the medical significance of evolved differences between mammalian species that the benefits to humans from experiments on rodents are at best highly indirect. These facts about animal experimentation and its relevance to human medicine need to be incorporated into the moral debates surrounding the use of animal models in the name of human well-being.

Species Differences versus Moral Similarities

The cases of medical-scientific research that we have discussed above involve attempting to address compelling human interests—the alleviation and avoidance of real human suffering that vitiates quality of life. Yet, that these benefits are advanced by using aminals as experimental subjects, is, in very many cases, not at all unquestionably established. In light of scientific questions about the reliability of animals as relevant causal analogs to humans, we have to see that likelihood of any benefit to humans is, as best a projected possibility in many cases of proposed research. This, we believe, compels rethinking appeals to utility to establish the moral permissibility of using animals as subjects in painful and/or fatal experimentation. And (more critically) we believe that there are reasons to believe that the only kind of moral arguments that could provide a justification for this practice, at least where there is no more or less certain remedial benefit to humans, would have to justify disregarding animal pain. But we, like many in the scientific community, find such arguments repelling, for reasons for which we will try to give voice in our epilogue.

Calculations of utility—of cost and benefit--loom so large in contemporary ethical debates, it repays our efforts to briefly reexamine the basic logic of utilitarian arguments for the permissibility of using animals as experimental subjects. The implications of evolutionary biology that we have noted render such arguments difficult even to formulate as genuine calculations of utility. Arguments for the moral permissibility of animal experimentation typically appeal to claims of great human benefit—historical or possible. In order for a utilitarian argument for the *permissibility* of any (sort of) action, A, to be plausible, it has to be possible to show, at a minimum, that A does not have actual (known and quantifiable) costs that outweigh uncertain (not knowable or quantifiable) benefits. In the case of animal experimentation, the cost in animal pain is actual, known, and

undoubtedly significant. It is significant even if, as Bentham originally suggested, animal pain is not poignant, psychologically complex, and so not of the duration of human pain. We do not have to assume Singer's principle of equality—that "suffering be counted equally with like suffering—insofar as rough comparisons can be made—of any other being"—to see that animal suffering is very real. The sheer number of animals used, and the ways in which they are used are unavoidable considerations in any meaningfully objective calculation of the utility of experimenting scientifically on live animals. The vast majority of animals used in research are rodents . But others include primates, dogs, cats, frogs, pigs, and pastoral animals. Many of them, if they are able to survive a specific episode or conditions of testing, are subjected to numerous episodes of suffering. Some research protocols require the use of very many animals. Rowan breaks animal use in laboratories into the following categories: education, drug discovery and toxicity testing, development and toxicity testing of other products, testing of biological agents, diagnosis, and research in biomedical science. (Shanks, 2002, 172.) We cannot deny that very many animals suffer what we can only regard as serious and repeated pain. Do they suffer and die in vain? (We have to be able to establish that there is a *definite* human benefit to countervale this undeniably great amount of animal suffering.

It is in the effort to establish that there is a real, measurable, and significant benefit to humans in animal experimentation that the implications of evolutionary theory become most significant. But, as a preliminary, more comments are in order about the requirements of utilitarian arguments for the justification of a (sort of) action. Questions of justification are more meaningful when we think about what would be required to show that *each specific test*, individually considered, involving live animals would be justified on utilitarian grounds. We need not purport to formulate an argument about the practice of using live animals in experiments *per se*—the strategy of animal rightists and liberationists who categorically oppose any use of living animals in laboratory tests that induce suffering. A successful utilitarian argument that it is morally justified to act in such a way as to prevent a future harm through actions that cannot but bring about other harms *has* to have *certain* benefits. And there can be no alternatives that would stand as good a chance to bring about equivalent benefits without inflicting equivalent harm. A clear justification requires not only that our expectation of benefit is at least likely to be fulfilled, it requires that we essentially can have no good reason to believe that an equivalent benefit can be produced by other means without equivalent harm. So in proceeding to tests involving live animals with a view to human benefit, we will always be weighing relatively well-known and quantifiable—and substantial--costs (harms to animals used) against uncertain benefits (which could possibly be procured by means less costly in terms of suffering). In cases of testing drugs for toxicity, carcinogenicity, or teratological outcomes (for example), in addition to animal tests, there are in-vitro tests, clinical studies, and other research approaches. Where there are alternatives, animal experimentation can be justified only if there can be no plausible reasons to believe as much might be learned by alternative means without the equivalent cost/harm in animal pain. The only benefits that could justify any particular experimental use of animals would have to be (a) at least very probable, and (b) benefits that could be obtained only by that means. The uncertainty of benefits, or the possibility that experimentation has misleading results make possible benefits to humans remote with respect to the real and quantifiable harms sustained by animal subjects of experimentation. So even very general preliminary reflections about calculating the utility of any experiment design that involves harming animals forces us to acknowledge that clear justification will almost always be difficult to demonstrate.

Appeals to utility to morally justify the *discounting* of animal pain, seem (in light of the implications of evolutionary biology) increasingly remote for another critical reason. If there is not a *certain* remedial benefit to humans, (that is, if there is any chance that for scientifically identifiable reasons that we have discussed), then that benefit is a probability (or merely a possibility, if it is only a possible, but not likely outcome). (1) Where a benefit is only probable, even if that probability can be quantified, it can never be calculated as a benefit against a cost that is certain, and can be expressed in meaningfully quantificational terms. There is simply nothing one can calculate, and (2) any talk of *discounting* animal pain (in the technical sense defined by Brody (2001) becomes unmeaningful. And finally, (3) where pain is then caused animals as experimental subjects (where a remedial benefit to humans is only an unquantifiable probability, however likely) their pain is really only being disregarded.

Let us assume that other conditions for appeals to utility as grounds for the moral permissibility of using animals as subjects in painful and/or fatal experiments have been met. Recall that discounting is the notion that a "unit" of pain counts less if it is experienced by animals than the same unit experienced by humans; as Brody notes, it denies the principle of equal consideration—that it is the "unit" of pain that determines the consideration it should be given in calculations of utility, and not who is the subject of it. In many proposed research protocols, the scope of animal suffering can be given a fairly precise quantification (number of animals, duration and intensity of suffering, fatality, etc.). But the benefit—human suffering that is remediated by knowledge gained (and only possibly gained) by means of the experiment—is unquantifiable in terms of the number of humans who will benefit, or whether there will be any benefit to any humans at all. Here, one has to be willing to act —to cause often significant pain to a significant number of animals without the certainty that there will be any remedial beneficial outcome for humans. There is, then, an unquantifiable probability that animals will suffer and die in vain, an outcome that is morally permissible only if animal pain may not only be discounted, but disregarded—i.e. if it is permissible even without a demonstrable benefit to humans.

Here, animals are being treated as "different in kind"—as "expendable" in ways that not even certain rule-utilitarians are at all likely to agree that human pain or life would be expendable. Where human lives or well-being are "sacrificed", a permissible "sacrifice" is for some demonstrable benefit for which it was not unreasonable to ask those who may enjoy that benefit to accept a small and equitably distributed risk of "sacrifice" in order that some benefit may be available. It is—for example--arguably not unreasonable to ask us to agree to forego access to organ transplants after the age of 65 in order that any pregnant woman (a far larger number of beneficiaries) have access to a full course of pre-natal care. The remedial benefit of universal pre-natal care is, of course, very great. We might find that it prevented more deaths and other forms of quality-of-life vitiating pain for a larger number of persons than providing organ transplants to everyone who needs them in order to live. We also know in advance (of agreeing to this policy) that there is a small chance we could be those whose need for a transplant organ will not be met, and we will be allowed to die. Rule-utilitarians would argue that under these conditions, it is not unfair to me, if I am the one who after 65 needs a liver, but am allowed to die. Here, we have a demonstrable and relatively quantifiable and certain benefit weighed against a small (relatively quantifiable) and equally distributed *risk*—equally distributed in the sense that no one can know in advance whether it will be themselves who needs the liver, so that the "price is paid" for the benefit by those to whom the cost is distributed by what is essentially a very low, but equal, stakes lottery. The "sacrifice" is just (it is

argued) because the risk was a foreseeable possible outcome of a policy it would not have been unreasonable for me to consent to. Even if we find such arguments compelling, animals "sacrificed" as subjects of painful and/or fatal experiments are not in a position analogous to that of the "sacrificed" human in this example. In the human case, rule-utilitarians insist that the "sacrifice" is just precisely by arguing that the principle of equal consideration is *not* violated—the risk of sacrifice and access to the benefit are arguably equally distributed. It is not a case of "discounting". If the human suffering to be remediated could be quantifed with respect (for example) to the number of subjects, duration, and some measure in intensity, there is also no reason to deny that it could be compared to the suffering entailed by the animals to be "sacrificed" in order to secure the remediation of human pain. The trouble is that with an only probable (i.e. not certain) remediation of human suffering, there is no way to specify a "quantity" or "figure" against which a quantification of animal suffering could be "weighed" for discount—or at least no one figure. And this possibility raises the question—*how "low"* could the figure designating remedial human benefit be (of possible outcomes of benefit) in order to justify the "sacrifice"—the "devaluing" of a quantifiably equivalent representation (if this is even possible) of animal suffering? Unless we would insist, at a minimum, that some (relatively quantifiable) benefit is a certain outcome of an research protocol where animals will be used as subjects of a painful and/or fatal experiment, then we imply that animal pain and death are permissible foreseeable outcomes of an experiment without *any* benefit—(since if a benefit is only probable, *no benefit* is also a *possible* outcome). And if "no benefit" is a possible outcome, then one "figure" designating "benefit" by comparison to which *any amount* of animal pain is permissible will be "0". And it follows that it can, in principle, be permissible to cause animals pain and/or death without a benefit.

One might respond that we have to have very good reasons for believing that there has to be a remedial benefit to humans that cannot be secured by any other means, where animals have to be used as subjects of painful and/or fatal experiments. But this is no good as a response. For the implications of evolutionary biology that we have pointed to show that the possibility that the benefit to humans of many experiments that entail significant suffering and death for animals is more likely to be "0" or negative (where more fruitful alternatives to animal experimentation went untried because using animals is, frankly, the path of least resistance). Even from a rule-utilitarian point of view, it would follow that the rule (the policy, if you will) of permitting ourselves to "sacrifice" animal well-being and lives where there is a less-than-50%-chance of remedial benefit to humans is wrong—because we could only reasonably expect following this rule to increase, rather than optimally diminish the overall amount of suffering that could be effected by human action.

Since there is only a possible (or probable) benefit to humans in by far the greatest number of proposed experimental protocols using animals as subjects of painful and/or fatal experiments, it has to be assumed—if it is deemed permissible to so use animals at all—that it is, in principle, permissible to cause them pain and/or death without any benefit as a certain outcome. Since, we feel certain, we would never agree that "sacrificing" humans (causing them very great—the "same amount of" pain and/or death) would be permissible—i.e would be "rational" for a potential subject to accept as a rational risk--where the beneficial outcome could be "0", animal pain is simply being treated (differently from humans) as though it may be valued at "0". If there is not *some* benefit that has to be certain, in order for causing a specific pain and death to a specified quantity of animals to be a justified "discount", then it is ultimately worth "O" units in human suffering. Here, we fail to see how "discounting" is different from simply disregarding animal pain. And the only sort of

honest moral argument that could justify it would presumably have to identify the animal difference (whatever that would be) from humans, that entails that it is permissible to cause any amount of animal suffering and death, even where the *actual* benefit to humans is "0".

Epilogue: a parting shot

We would suggest, following G. J. Warnock's well-known assessment of the "general object" of morality, that acting against the presumption that we should never intentionally cause pain (to any being who acts as a 'kind' as though it is the subject of pain) where there is no certain and relatively quantifiable benefit to humans--carries a grave moral risk.

Now, the general suggestion that (guardedly) we wish to put up for consideration is this: that the 'general object' of morality, appreciation of which may enable us to *understand* the basis of moral evaluation, is to contribute to betterment- or non-deterioration- of the human predicament, primarily and essentially by seeking to contervail 'limited sympathies' and their potentially most damaging effects. It is the proper business of morality, and the general object of moral evaluation, not of course to add to our available resources, nor- directly anyway- to our knowledge of how to make advantageous use of them, nor again, not directly – to make us more rational in the judicious pursuit of our interests and ends; *its proper business is to extend our sympathies, or better, to reduce the liability to damage inherent in their natural tendency to be narrowly restricted*. (Italics inserted.)

The argument that we advance here is essentially the simple claim that our limited sympathies cannot be extended so as to 'reduce the liability to damage' inherent in our 'natural tendency to be narrowly restricted' without them extending to human actions that damage and cause pain to non-human animals. In particular, our argument will consist in a specific view about what it would mean to "extend" our sympathies.

At the level of our basic encounters with animals, we explain much of their "behavior" as actions, and not merely mechanical response-stimuli. Our 'ordinary language' about the actions of animals, and their interactions with us (especially, but not only, if they are pets or domesticated animals) cannot but attribute mental states to them that are "about" objects in the world, including their own bodies. Descriptions of animal behavior rich enough to do justice to our full engagement with many species of animals will typically attribute to them desires, and complex and cognitive emotions such as fear, anger, sometimes grief—even if we seek to avoid anthropomorphism.

The language that we must use is that with which we attribute apparently analogous states to human beings. As Thomas Scanlon points out, "With our pets, for example, we may value taking ourselves to have a relationship modeled on that between humans, a relationship involving mutual expectation, reciprocated affection, and emotions such as disappointment, anger, and even resentment. This involves attributing to the animal capacities that go well beyond (being conscious and capable of feeling pain)." (Scanlon 1998, 182.). Such talk would be merely quaint if it were not for the fact that explanations of animal behavior that attributes emotions, something like beliefs, and other intentional mental states to animals have significant predictive power—in both informal and controlled contexts. Talk of predictive power seems almost too abstract; where humans have intricate emotionally participatory relationships with animals, animals' guardians and companions are typically able to predict responsive actions of animals with great precision by attributing their

actions to them in terms of the language of “folk psychology.” Human interaction with those animals cannot but take account of the claims we make (the beliefs that we form and express) about animal “behavior” in terms with which we also describe much human behavior. And the beliefs about animal minds and experiences we must form in order to interact with animals at all—in either controlled or ‘informal’ and unintentional environments—can only be expressed in this language which at least implicitly attributes intentional mental states to them.

Some have been tempted, here, to appeal to skeptical arguments about animal pain- and self-consciousness. There are, however, deep moral reasons why we would not want skepticism about animal pain-consciousness and other intentional states to defeat our ordinary interpretations of the expressive and evasive actions of animals in the presence of real harms—even if skeptical arguments cannot be defeated. Moral autonomy presupposes the capacity to form some justified beliefs about “other minds” (and perhaps the states of those minds as response to realities in their environment) even if they only *behave as if* they feel pain, fear, anger, hunger, desire, etc. that are responses to features of their environment. And if we are sensitive to, and justified in believing that, a human is in pain, and are moved by perception/belief to appropriate action, then we cannot but be moved by comparable expressions of animal pain when we confront it in experience. By ‘comparable’, we mean to call attention to the obvious fact that humans and many other animals signal distress and pain in many of the same ways.

A wide range of responses to pain, as well as expressions of emotion, are language-like in the way that they lend themselves to interpretation. They partake of shared “non-private” codes of meaning, the learning of which is a necessary condition for having the capacity to form justified beliefs about others’ feelings, etc. More specifically, we only *understand* the situation of other persons and non-human animals if we can “read” their expressions of pain (or of emotion) in a way that parallels spontaneously grasping the meaning of linguistic expression. (This claim, we would argue, is analogous to the fact that I can’t understand what you mean by uttering “yellow”, yet fail to understand what someone else means by it, if they follow the same rules in using it to assert a claim about another object.) If we can understand such expressions, then, to the degree that animal behavior appears to consist in expressions of pain and emotion, we cannot but intuitively attribute parallel (if not identical) meanings to certain apparently parallel animal expressive behavior, in relevantly similar circumstances.

The presumably unique human capacity to verbalize pain linguistically does not diminish this critical parallel between animal and human expressions of pain and responses to harms and perceived threats of harm. Animal pain is, of course, as subjectively “private” as any human pain experience. We attribute pain to animals because we interpret cries of distress and aversive behavior by reference to our own memory of pain, fear, and seeking to remove ourselves from perceived harms—indeed human and animal expressions of pain, and aversive responses such as the expression of fear and taking flight are *homologous*—i.e. the same in terms of meaning.

It follows that a failure of appropriate cognitive and interventional response to the appearance of animal pain has to constitute just as much a failure of understanding (of forming justified beliefs) under the conditions that demand it, as it would constitute in a failure to respond to a parallel human subject. (Again, we are only said to understand “yellow” to the degree that we can grasp the meaning—know how to determine the epistemic justification of any proposition attributing it to an object—when it is uttered by *any* speaker. And if we know in one case, then we will know in any

case of its use.) In the case of other humans, we would regard such a failure to grasp the meaning of pain expression as a failure of understanding (not being able to know that it is pain that is being expressed, or of sanity (pathological). It cannot be the case that we can have the capacity to form justified beliefs about whether other humans are experiencing pain, but not also have the capacity to form justified beliefs about whether other animals are experiencing pain—skepticism about animal consciousness notwithstanding. So if we fail to notice and respond to the pain of non-human animals, then there is every good reason to doubt that our response to human pain can be counted on when it is morally critical that we exercise this capacity. It is "pain expressing behavior", precisely the "appearing as if" in pain *itself* that we have to be 'sensitive' to in order to be able to form justified beliefs about others' (humans' and animals') intentional mental states.

Encounters with pain-expression in the conduct of others (human or nonhuman), with even a minimal capacity for sympathy or compassion, mobilizes our own spontaneous emotional and motivationally salient responses. Pain sensation, for both humans and non-human animals, targets and "tracks" harms, and motivates 'avoidance behavior'. These harms may be physical conditions that portend destruction of the body or interrupt vital functions. Let us begin with the assumption that *ought* implies *can*. In order for a course of action to be open to us (in order to be able to intend and choose it), we have to know about it. In many cases which we would regard as tests of moral autonomy itself, we can only be responsible for acting or failing to act if we can be aware, and form justified beliefs about, the actual or possible mental states of other subjects. This arguably applies not only to being able to form justified beliefs about pain, but also other mental states such as the emotion of fear, and whether that fear is merited by its object. Otherwise, we would be *unaware* that the circumstances of another subject call for me to act in a way that we might otherwise regard as morally critical (or refrain from acting)—that her pain, or the harm that brings it about, would be cuased or alleviated by a specific action that we are committing.

We have come to *value* the capacity to recognize the mental states of others, as well as the predisposition to alleviate harms to others (and to bound one's own action with reference to the harms others would suffer as a foreseeable consequence) as virtues (excellences of character arguably necessary for human flourishing). We form second-order desires that a range of first-order feeling- and action- responses occur under circumstances that merit them. Ronald De Sousa (1987) makes this point well in reference to a range of emotions.

According to this *diagnostic use of consistency*, the decisive question is not about constancy. It is whether one is committed to the second-order desire that the first-order emotion recur under relevantly similar conditions. If it does, that marks you as recognizing the possibility of "relevantly similar conditions." And that is all there is to the claim of universalizability: Only those emotions are *subjective*, in addition to being *agent-relative*, which do not acknowledge the claim of consistency.[2]

We take it nothing is less controversial than that we are counting on, have to count on, others to be able to know (through reading our expressive behavior) when their actions or other causes bring us harm or cause us pain. And our ability to know pain when we see it, and to respond with any of a wide range of motivationally salient feeling-responses attuned (as it were) to "relevantly similar circumstances", has to be *objective* (or *intersubjective*) and *agent-neutral*.

The consequence for evaluating the justification of using animals experimentally is that on the one hand, we have to want experimenters to be aware of animal pain and alleviate it—yet to ignore it as a matter of fact—in the interest (we suppose) of a greater human good or benefit. So far, we have good grounds for supposing "insensitivity" to animal pain is either pathological or vicious. But this is far from a moral prohibition against using animals as experimental subjects.

Warnock suggests that the purpose of "morality" is to "mitigate to some degree the ill effects that are inherently liable to flow from the indifference of persons to other (persons)."[3] Our argument is that if moral motivations find their most fundamental source in our ability to know, and predisposition to respond to, the suffering of any being who appears to be capable of suffering, then denial of the appearance of suffering, and the predisposition to alleviate it in any subjects we encounter, defeats moral motivation per se—defeats the very motivations that we claim motivates experiments aimed at betterment for humans.

Summary

Of what moment are benefits to humans of using animals as subjects of experimentation? The first part of our essay suggests that since animals can rarely be demonstrated to be genuine causal analogs of human beings (in, for example, toxicological tests, as ours examples suggest), experimental benefit to humans (either in the "growth" of knowledge or prevention of human exposure to toxins, for example) is almost always very uncertain. We are no longer discovering the macro-mechanical anatomical functions that human and animal bodies seemed to share in the eyes of the 19th century physiologists who promoted the practice of experimenting upon (and dissecting) often living animal bodies as a way to understand human bodies. The knowledge gained from such experiments has undoubtedly advanced our understanding of the function of the human body in countless ways. But if it has any parallel in current practice, it would be testing certain surgical procedures on animals. One example might be the recent test on pigs of a surgical procedure to correct short bowel syndrome in humans. Such a test, in contrast to many of the examples we discussed in the first part of our paper, proceeds on the basis of a clear knowledge of precisely how digestive function in the intestines of pigs is causally analogous to the digestive function of human intestines. In such a case, it is possible to reliably predict benefits to humans both in respect to the elimination of risk, and determining corrective benefit. Xenotransplantation raises additional questions about the conditions under which animal pain may be discounted to benefit humans. The calculation of benefit to humans (if a procedure worked) would seem to be less troublesome than in cases where questions arise about the reliability of members of an animal species as reliable causal analogs to humans; though this discounts real worries about transmission of porcine endogenous retroviruses from pigs to humans. Arguments for these cases of using animals as subjects in painful or fatal experiments at least may put forward a significantly certain benefit, or reliably eliminate a very real risk to humans. In any case, however, where the calculation of benefit is uncertain (even if possible, in some abstract sense), we have suggested that the discounting of animal pain requires experimenters to "bracket" responses to pain that we must otherwise value as a critical part of a fundamental moral virtue. This consideration would also set limits on the benefits to humans for which animal pain could be discounted. Roughly, the limit must be understood as follows: Since discounting animal pain necessarily requires (as a condition) bracketing responses to pain that are critical elements in human moral autonomy and flourishing, no human need that bears less weight that this one, in any estimate of the value of certain virtues in human well-being, should over-ride

the prohibition against discounting animal pain. Hence, for example, testing cosmetological products on animals for safety to humans, where the tests clearly cause animal suffering, would always be morally unjustifiable. Proposed experiments without a demonstrably certain benefit, however, (where questions can be raised about the reliability of the species experimenters propose using as causal analogs to humans) cannot be justified by calculations of utility, and so the suffering that animals would endure is really being treated as permissible in principle (permissible even where there may be no benefit to humans). Here, the experimenter has to countervale the very motivations that lend human value to her scientific enterprise—to be reliably motivated to mitigate human suffering.

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Notes

1. LaFollette and Shanks, (1996), 254ff.

2. De Sousa (1987), 311.

3. Warnock (1971), 149ff.
